Full title: Feasibility of computerised adventitious respiratory sounds to assess the effects of airway clearance techniques in patients with bronchiectasis.

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ABSTRACT

Objective To examine the feasibility of adventitious respiratory sound (ARS) as an outcome measure to assess the effects of airway clearance techniques (ACTs) in outpatients with bronchiectasis.

Methods ARS were registered pre/post four ACTs sessions. Clinical outcomes included: number of crackles (coarse and fine), number of wheezes (monophonic and polyphonic), wheezes occupation rate (%) and sputum quantity. Feasibility outcomes of ARS included: reasons for exclusion, suitability, safety, equipment and time required, magnitude of change after intervention and sample size estimation.

Results Seven patients (49.7±20.5yrs; FEV_1 69.3±15.8% predicted) were included. Recordings from four patients were excluded due to excessive environment noise. All ARS measurements were completed without any adverse events. An electronic stethoscope was acquired and the time spent to complete each assessment was 6±3.5min. The largest changes were observed for number of expiratory coarse crackles [effect size(95%CI) ES=0.40(0.01-0.79)], which correlated moderately with sputum quantity (r=0.56), and inspiratory monophonic wheezes [ES=0.61(0.22-1.00)]. The estimated sample size for a full crossover trial was 46.

Conclusions ARS is feasible to assess the effects of ACTs in patients with bronchiectasis. Expiratory coarse crackles seem to be the most appropriate ARS parameter, but this finding needs to be confirmed in an adequately powered trial.

Keywords physical therapy, bronchiectasis, respiratory sounds, rehabilitation, airway clearance techniques.

Abstract word count 198

Manuscript word count 3780

References 37

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INTRODUCTION

Airway clearance techniques (ACTs) are recommended for patients with bronchiectasis, by the recent European guideline aiming at improving sputum expectoration (Polverino et al, 2017). Nevertheless, the level of evidence of ACTs is still poor (weak recommendation and low quality of evidence) (Polverino et al, 2017; Lee, Burge and Holland, 2017), mainly due to the limitations of the available measures (Bradley, O´Neill, Vilaró and Mcllwaine, 2018; Marques, Bruton and Barney, 2006), such as subjectivity (e.g., conventional auscultation), unstandardized and challenge procedures (e.g., sputum volume) and lack of sensitivity to detect small changes (e.g., lung function). Therefore, the selection of outcome measures to assess ACTs effects and the interpretation of its results should be carefully performed, as they may hamper establishing the effectiveness of ACTs.

Computerised adventitious respiratory sounds (ARS), such as crackles and wheezes, are objective, simple and non-invasive outcome measures (Marques, Bruton and Barney, 2006), that have been associated with the presence of excessive airway mucus and bronchial obstruction (Bohadana, Izbicki and Kraman, 2014; Piirilä and Sovijärvi, 1995). Given the potential of ARS to be used as outcome measures to assess airway clearance or bronchial obstruction, previous studies have been exploring ARS responses to different interventions in respiratory diseases (Marques, Oliveira and Jácome, 2014).

ARS have shown to be reliable and valid to be used in patients with bronchiectasis (Marques, Bruton and Barney, 2009) and other respiratory conditions (Jácome and Marques, 2015; Oliveira, Lage, Rodrigues and Marques, 2017a). However, it is still unclear what parameter of crackles and wheezes are the most appropriate to evaluate

the effects of ACTs and what direction and magnitude of change corresponds to a clinical improvement in patients with bronchiectasis. Moreover, according to the authors' best knowledge, the correlation of computerised ARS after ACTs with changes in other clinical outcomes, such as the amount of sputum collected, has never been explored, limiting the interpretation of the results achieved (Mokkink et al, 2009). Thus, before conducting an adequately powered definitive clinical trial using computerised ARS as an outcome measure for ACTs in patients with bronchiectasis, a preliminary study assessing the feasibility of this outcome measure is needed to ensure greater accuracy of the results achieved.

This study aimed to determine the feasibility of computerised ARS as outcome measure in patients with bronchiectasis by: i) exploring the suitability and safety of ARS measurement procedures; ii) assessing the time required to complete the ARS registration; iii) describing the equipment required and their cost; iv) exploring the direction and magnitude of changes after four sessions of slow-expiratory ACTs; v) evaluating the correlation between changes in ARS and sputum expectorated after slow-expiratory ACTs; vi) estimating the parameters required to calculate the sample size for a future definitive randomised crossover trial (RCT). The authors hypothesised that the mean number of crackles, the mean number of wheezes and wheezes occupation rate (%) per respiratory phase (inspiratory and expiratory phase) will change significantly following the ACTs treatment (Marques, Oliveira and Jácome, 2014; Oliveira, Pinho and Marques, 2015) and these changes will have a positive and moderate correlation with the amount of sputum expectorated during ACTs treatment in patients with bronchiectasis.

METHODS

Study design

A prospective repeated measures feasibility study, part of a randomised crossover trial (NCT01854788) (Herrero-Cortina et al, 2016), was conducted. Ethical approval was obtained from the Hospital Clinic Research Ethics Committee (HCP/2010/215).

Participants

Adult outpatients diagnosed with bronchiectasis by high-resolution computed tomography (HRCT) scans were recruited from a community hospital in Barcelona (Spain) between October 2011 and June 2013. The inclusion criteria were evidence of moderate daily sputum production (≥15ml, based on classification previously proposed by King et al. (2006)), being clinically stable for 6 weeks before data collection (defined as no need for extra antibiotics or changes in usual therapy) (Murray et al, 2011) and having training in the performance of slow-expiratory ACTs (slow expiration with glottis opened in lateral posture - ELTGOL and autogenic drainage - AD). Patients were excluded if they were smokers, had severe lung function impairment (forced expiratory volume in one second percentage predicted - FEV_1 ≤30% pred. and forced vital capacity percentage predicted - FVC ≤45% pred.), were not allocated to receive ELTGOL and AD at the beginning of the main study, experienced an exacerbation of their respiratory condition during the study period and presented poor quality of ARS recordings (i.e., artefacts or environment noise) (Rossi et al, 2000), which negatively affects the analysis. Prior to any data collection, written informed consents were collected from all participants.

Intervention

The intervention consisted in 4 airway clearance sessions performed in two non-consecutive weeks at hospital. The first two sessions were performed in the first week (at least 48-h period apart), and the remained sessions were performed in the third week. During the second week, no physiotherapy treatment was performed (a 7-day washout period). For the purposes of this study, repetitive sessions were analysed to ensure greater accuracy of the results (figure 1).

All patients performed ELTGOL and AD techniques (two times in the same week) in a random order (ELTGOL/AD or AD/ELTGOL; figure 1) according to the recommendations (Agostini and Knowles, 2007; Martins et al, 2012,). In the current study, the ELTGOL and AD techniques were both chosen to assess the feasibility of computerised ARS to slow-expiratory ACTs because both are based on the same physiological action, i.e., decrease of the cross-sectional ratio of medial and peripheral airways without dynamic compression to increase the airflow velocity in these areas (McIlwaine, Bradley, Elborn and Moran, 2017; Wong, Sullivan and Jayaram, 2018), and have shown equal efficacy (similar level of expectoration after the application of each technique) in patients with bronchiectasis (Herrero-Cortina et al, 2016).

Sessions lasted 40 minutes (during ELTGOL sessions, participants spent approximately 20 minutes in each decubitus) and were applied by one trained physiotherapist in a standardised schedule.

(please place figure 1 around here)

Clinical data collection

A trained physiotherapist conducted all data collection. One week prior to the intervention, patients' sociodemographic, anthropometric and clinical data (aetiology of bronchiectasis, radiological severity and lung function and quality of life) were collected. Computerised ARS were recorded immediately before and after each of the four airway clearance sessions (Session A, B, C and D; figure 1) in a single room at hospital. Recordings were performed according to the Computerised Respiratory Sound Analysis (CORSA) guidelines for short-acquisition (Rossi et al, 2000). Participants were in a seated-upright position and respiratory sounds were collected with a hand-held electronic stethoscope (3MTM Littmann®, Model 3200). Sequential 15-second recordings were performed in seven chest locations (right and left: posterior, lateral, anterior chest and trachea; figure 1). During data collection, the sounds were transmitted, via Bluetooth®, and stored in a computer in .wav format.

All sound files were analysed using automatic validated algorithms (Huq and Moussavi, 2010; Pinho et al, 2016; Taplidou and Hadjileontiadis, 2007) implemented in Matlab 2009 (The MathWorks, Inc, Natick, MA, USA) to detect and characterise respiratory phases and ARS.

The parameters extracted from crackles were: mean number of crackles (total, coarse and fine) per respiratory phase (inspiration and expiration). Trachea was excluded from the crackles analysis due to its poor reliability observed in previous data (Jácome and Marques, 2015; Oliveira, Lage, Rodrigues and Marques, 2017a). Mean number (total, monophonic and polyphonic) and occupation rate of wheezes (%) per respiratory phase

were extracted from wheezes, including trachea point in the analysis (Jácome and Marques, 2015).

The amount of sputum obtained (g) was assessed using two pre-weighted containers, one to weigh the wet sputum expectorated during each airway clearance session and the second to collect the spontaneous sputum obtained over the 24h period after the sessions (Herrero-Cortina et al, 2016). All Participants were instructed to avoid salivary contamination and secretions from sinus were not allowed to include in the containers.

Feasibility of computerised ARS

The suitability of ARS assessment was evaluated based on completion rate, rate of missing data and reasons for exclusion or dropouts due to the procedure. The cost of the additional equipment required was also calculated (expressed in Euros) to complete the feasibility analysis for clinical practice. Safety was explored by describing the number and type of adverse events which occurred during recordings, and the time needed to complete the assessment (including instructions) was measured in minutes. With no clear existing criteria, the feasibility criteria for computerised ARS were: completion rate assessment ≥ 80%, less than 20% of missing data from data extracted, no dropouts nor adverse events due to the procedure, and the total time (pre and post measure) did not exceed the airway clearance session.

Statistical analysis

This feasibility study was not powered to determine differences in computerised ARS after ACTs, thus, hypothesis testing was not undertaken (Lancaster, Dodd and Williamson, 2004; Orsmond and Cohn, 2015). Accordingly, the results were only focused

on describing and estimating the treatment effects to offer insights to guide the future definitive RCT.

Baseline characteristics of participants and feasibility outcomes were summarised descriptively. The ARS characteristics were described for each of the sessions performed and global ARS findings were stratified for each one chest location recorded (trachea, anterior, lateral and posterior). For this purpose, right and left locations were pooled (Jácome, Oliveira and Marques, 2015; Oliveira et al, 2017b). The pre and post findings of the four sessions were included in the analysis to increase the accuracy of the results. Differences in crackles and wheezes parameters pre and post sessions were explored and results were expressed as median difference and 95% confidence interval (95%CI) (Altman, Machin, Bryant and Gardner, 2000). Effect sizes (ES) were also estimate using rank-biserial correlation (Wendt, 1972) and 95%CI (Nakagawa and Cuthill, 2007).

To establish the most appropriate ARS parameters to assess airway clearance, the ARS presenting the highest ES (one specific acoustic parameter of crackles and one of wheezes, to avoid multiple correlations that increase the risk of Type I error (Feise, 2002)) were selected and correlated with the sputum quantity ratio (%) (i.e., sputum expectorated during the session/ 24h overall sputum obtained x 100) using Spearman´s rank correlation. Correlation values were interpreted as weak ($r \leq 0.29$), moderate ($0.30 < r \leq 0.59$), and strong ($r \geq 0.60$) (Domholtd, 2010). Finally, the variability and the change observed from these ARS parameters selected were used to estimate the sample size needed for a definitive trial.

Data analysis was performed using SPSS v.19 (IBM, Chicago, IL, USA) and plots were created using GraphPad Prism version 5.01 (GraphPad Software, La Jolla, California, USA).

RESULTS

From the 31 participants randomised in a larger trial (Herrero-Cortina et al, 2016), eleven were allocated to receive ELTGOL-AD or AD-ELTGOL at the beginning of the trial. All participants accepted and completed all ARS measurements without the occurrence of adverse events. Only one participant, who presented the major lung function impairment (FEV_1% pred.= 41), needed pauses between the recordings. Data rates extracted from the recordings were excellent (100%) without missing data; however, the quality of data from four participants was low due to excessive environmental noise and had to be excluded. Thus, only seven participants and their characteristics are shown in Table 1. Three participants started with ELTGOL and four started with AD. The sputum quantity ratio obtained during sessions was 39% (see supplementary material, Table A).

(Please Table 1 around here)

The additional equipment required was only a hand-held electronic stethoscope because the computer used belonged to the physiotherapy department. The cost of the stethoscope was estimated around 380€ (based on 2011 prices). The physiotherapist spent 6±3.5 min to complete the seven chest locations recordings for each evaluation session and a total of 392 respiratory sound files from all anatomical locations were analysed. Table 2 shows the descriptive characteristics of ARS for each of the four

sessions, including all chest locations recorded. Table 3 presents the global ARS findings stratified by each chest location recorded.

(Please Table 2 and 3 around here)

Crackles findings

After slow-expiratory ACTs, the mean number of inspiratory and expiratory crackles increased, except in the first session, with coarse crackles the main ARS responsible for these changes (see Table 2). Inspiratory coarse crackles increased mainly in anterior and posterior regions whilst expiratory coarse crackles decreased in anterior regions and increased in lateral and posterior regions, after the sessions (see Table 3).

Considering participants' individual results, after the airway clearance session, four participants experienced an increase in the amount of inspiratory coarse crackles whilst the remaining three did not show any change. Six participants showed an increase in expiratory coarse crackles after slow-expiratory ACTs. A heterogeneous direction of change was observed for fine crackles (see supplementary material, figure A).

Wheezes findings

The total number of wheezes and monophonic wheezes increased after intervention in all sessions, whilst no changes were observed for polyphonic wheezes (see Table 2). Similarly, increases in the wheeze occupation rate were observed after intervention, mainly during expiration. The increase in the number of inspiratory wheezes were similar across all chest regions; however expiratory wheezes and wheeze occupation rate increased mainly at the trachea (see Table 3).

Considering participants' individual results, after the airway clearance session, the number of monophonic wheezes increased in six participants during inspiration, and in four participants during expiration. Most participants also showed an increase of polyphonic wheezes after treatment (five during inspiratory phase, and four during expiratory phase) (see supplementary material, figure A).

Correlation between ARS and sputum expectorated

The number of expiratory coarse crackles and inspiratory monophonic wheezes were the computerised ARS parameters which experienced the major changes after the intervention (see table 4), and thus were chosen for the correlation analysis.

(Please Table 4 around here)

A moderate positive correlation was observed between the increase of expiratory coarse crackles and the sputum quantity ratio (r=0.56), whereas changes in inspiratory monophonic wheezes presented a negative and small correlation with the sputum quantity ratio (r= -0.18) (see Figure 2). Thus, expiratory coarse crackles seem to be the most appropriate primary outcome measure.

(please place figure 2 around here)

Sample size estimation for future trials

Crackles and wheezes have showed high inter-subject variability in bronchiectasis and other respiratory disease(Jácome and Marques, 2015; Marques et al., 2009). Therefore, a randomised crossover trial might be the study design most appropriate(Mills et al, 2009) to assess the short-term effects of ACTs using computerised ARS as an outcome

measure. The mean (SD) of the difference in response to slow-expiratory ACTs by the same participant in this study was 0.58 (1.23) for expiratory coarse crackles. Based on this assumption, an alpha risk of 0.05 with 80% power, in a two-sided test, it is estimated that a sample size of 38 participants will be required in future crossover trials. Considering a common drop-out rate of 20%, the final sample size required for future studies would be 46 participants.

DISCUSSION

According to the authors' best knowledge, this is the first study to determine feasibility of computerised ARS to slow-expiratory ACTs as an outcome measure in a small sample of stable patients with bronchiectasis. The main findings were: (1) computerised ARS presented acceptable feasibility in terms of completion rate, missing data, safety, cost and the time taken to complete the ARS registration. However, environment noise negatively influenced the quality of data extracted from four patients and is potentially the main barrier of the assessment procedure; (2) the number of expiratory coarse crackle and inspiratory monophonic wheezes were the ARS parameters that experienced the major changes after slow-expiratory ACTs; (3) differences in expiratory coarse crackles correlated positively and moderately with the sputum quantity ratio collected during sessions.

Based on our findings, computerised ARS seem to be a feasible outcome measure for use in clinical practice and future studies in patients with bronchiectasis. Nevertheless, achieving an optimal background noise level (below 60 dB) (Rossi M et al, 2000) within a hospital environment appears to be a barrier for ARS recording. For practical purpose, it is recommended to choose a room with less transient noise with appointments

schedule during quieter times. The only additional equipment required (electronic stethoscope) and its cost may be acceptable for clinical practice and future research with low funding.

Globally, the mean number of expiratory crackles after slow-expiratory ACTs increased and this pattern was presented in six out of the seven participants involved in this study. Oliveira, Pinho and Marques (2015) observed similar results after one single session of physiotherapy with slightly lower ES (pre 2.64±1.68 *vs.* post 3.22±1.99, ES=0.31) in obstructive patients with lower respiratory tract infection. These findings might suggest that the direction of crackles change is towards an increase after ACTs sessions. However, our findings contrast with those reported by Marques, Bruton, Barney and Hall (2012), who suggested that the mean number of crackles is not able to change after one session of ACTs in patients with bronchiectasis. Although the target population included in both studies was similar and presented a comparable pre-intervention number of crackles (4.14±2.31 *vs*. 5.55±2.19 in our study), the ACT performed were different (active cycle of breathing technique *vs* ELTGOL/AD in our study). Also, the time period of the session was shorter for Marques, Bruton, Barney and Hall (2012) study (average of 24 minutes *vs.* 40 minutes in our study) and the data was based only on a single session (*vs.* repeated measured in our study) which may justify the differences found.

It is known that slow-expiratory ACTs enhance mucus clearance from small/medium to larger airways (Button and Button, 2013). The motion of intraluminal mucus to larger airways produces a major airflow in small/medium airways and this process may allow a sudden reopening of abnormally closed airways, which in turn might generate an

increased number of crackles (Oliveira, Pinho and Marques, 2015). In our study, most changes occurred in the number of expiratory coarse crackles which were also correlated with the sputum quantity ratio, whereas inspiratory coarse crackles and fine crackles remained almost unchanged presenting a heterogeneous direction of change among participants (i.e., some participants presented increases and other presented decreases).

It is believed that obstructive diseases are associated with early inspiratory coarse crackles, and thus the present data is consistent with the concept that inspiratory coarse crackles depend mainly on the pathophysiology of the surrounding tissue (Piirilä and Sovijärvi, 1995), whereas expiratory coarse crackles seem to be able to respond to short-term effects of ACTs in stable patients with bronchiectasis. Therefore, for a future RCT in patients with bronchiectasis, expiratory coarse crackles might be the most appropriate primary endpoint.

Similar to crackles, the mean number of wheezes also increased after sessions. Inspiratory monophonic wheezes was the parameter that changed the most after the treatment, increasing in six participants; however poor correlation with the sputum quantity ratio collected during intervention was found. Otherwise, the occupation rate of wheezes presented a slightly change after treatment, suggesting that despite the increased wheezes, the level of obstruction remained almost unchanged. The higher number of wheezes after the session, specifically observed at the trachea, could be associated with the number of forced expiratory manoeuvres (cough) performed. The relationship between wheezes and forced expiratory manoeuvres has already been shown in patients with asthma and COPD (Fiz et al, 2002); however no studies have been

performed in patients with bronchiectasis. It is possible that the same mechanism may be observed in this population. Nevertheless, as the numbers of cough manoeuvres were not registered and computerised ARS were recorded at the end of the session, definite conclusions cannot be drawn.

Previous data on the behaviour of wheezes after physiotherapy interventions in adults is limited to a pre/post study conducted by Oliveira, Pinho and Marques (2015) in patients with lower respiratory tract infections. These patients performed a protocol composed of breathing techniques to enhance sputum expectoration (20-25min.), exercises to increase pulmonary volumes (15min.) and education (15min.). Considering all chest locations, no differences in the mean number of wheezes and wheeze occupation rate after the intervention were found in the subgroup of patients with obstructive diseases (Oliveira, Pinho and Marques, 2015). These different results may be related with the higher inspiratory volumes associated with the exercises performed after the ACTs, which helped reverse the airway collapse related to cough manoeuvres, or due to the different timing of computerised ARS recordings (after the physiotherapy session vs immediately after the ACTs in this study).

A sample of 46 participants would be required for future crossover trials using expiratory coarse crackles as the primary outcome measure. Assuming that the rate of recruitment in previous crossover trials evaluating short-term effects ACTs in bronchiectasis was around 65% (Herrero-Cortina et al, 2016; Paneroni et al, 2011), at least 71 eligible patients would need to be invited to take part in a future study.

Limitations and Future work

The results of this feasibility study should be interpreted with caution particularly due to the small sample size included. However, the study was designed to maximise the accuracy of the findings as repeated measures were performed in four non-consecutive physiotherapy sessions.

Equipment to standardise airflows and volumes were not acquired and this may have affected the results on crackles and wheezes parameters. However, this study focused on analysing the feasibility of an outcome measure to be easily applied in clinical practice (Marques, Bruton, Barney and Hall, 2012). Despite the chest locations were recorded individually with only one stethoscope, the time burden was low and generally well tolerated. Future trials might be included two recordings for each one chest location in order to improve the results accuracy.

Participants with lower probability to generate enough airflow (i.e., severe lung function impairment) were excluded from the present study to ensure greater quality of ARS recordings. Future studies evaluating the tolerability of ARS recordings in people with bronchiectasis and severe airflow obstruction should be conducted to test the feasibility of using this measure also in severe patients.

Further studies are required to explore if other parameters, such as normal respiratory sounds, i.e., intensity and frequency, are able to respond to slow-expiratory ACTs. It is also recommended to study the measurement validity and responsiveness of computerised ARS and the most appropriate time point to record the ARS after a session in patients with bronchiectasis. Finally, building on the findings of our study, future larger studies are needed to explore whether ARS are also an appropriate outcome to

assess long-term efficacy of ACTs and for comparing the effects of different ACTs on ARS changes.

CONCLUSION

These preliminary findings support the feasibility and potential use of computerised ARS as an objective and simple clinical outcome to assess the short-term effects of slow-expiratory ACTs in patients with bronchiectasis. The mean number of expiratory coarse crackles and monophonic inspiratory wheezes were the ARS parameters that appeared to change after an intervention. However, only changes in expiratory coarse crackles correlated with sputum quantity ratio, highlighting the usefulness of this parameter to assess the effects of slow-expiratory ACTs in patients with bronchiectasis.

ACKNOWLEDGEMENTS

The authors' grateful acknowledge the contribution of 3M™ Littman® in providing the electronic stethoscope used in the respiratory sounds evaluation. The authors are also very grateful to all patients for their participation in this research study.

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TABLES

Table 1. Participants' socio-demographic, anthropometric and clinical characteristics (n=7).

Patients' characteristics	**n=7**
Gender (male)	1 (14 %)
Age (years)	49.7 ± 20.5
BMI (Kg/m^2)	24.1 ± 3.8
Aetiology of bronchiectasis	
– Primary ciliary dyskinesia	2 (28 %)
– Associated COPD	1 (14 %)
– Secondary immunodeficiency	2 (28 %)
– Idiopathic	2 (28 %)
No. of lobes affected by bronchiectasis	4 ± 1.7
Chronic airway infection	
– *Pseudomonas aeruginosa* infection	3 (42.8%)
Lung function	
– FEV_1 % pred.	69.3 ± 15.8
– FVC % pred.	85.2 ± 18.0
– FEV_1/FVC	66.5 ± 4.5
St George´s Respiratory Questionnaire total score	44.6 ± 9.4

Data are presented as number (percentage %) or mean ± standard deviation

Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease; FEV_1 %pred. , forced expiratory volume in one second percentage predicted; FVC % pred. , forced vital capacity percentage predicted.

Table 2. Descriptive characteristics of adventitious respiratory sounds for each one of the four airway clearance sessions.

	Session 1		Session 2		Session 3		Session 4	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post
Number of Crackles†								
Inspiratory phase								
Total	1.62[1.27-2.52]	2.31[1.43-3.00]	1.56[1.19-2.78]	1.80[1.25-1.97]	1.77[1.37-2.83]	2.06[1.43-2.19]	1.83[1.25-2.61]	2.08[1.36-2.47]
Coarse	1.48[1.13-1.75]	1.98[1.36-2.19]	1.43[0.97-1.91]	1.55[0.94-1.77]	1.58[1.20-1.73]	1.44[1.33-1.90]	1.58[1.13-2.23]	1.47[1.33-2.27]
Fine	0.16[0.13-0.26]	0.33[0.08-0.83]	0.29[0.21-0.44]	0.30[0.25-0.41]	0.33[0.16-0.43]	0.41[0.13-0.50]	0.26[0.14-0.47]	0.25[0.01-0.50]
Expiratory phase								
Total	3.29[2.06-4.50]	2.88[2.30-6.22]	3.52[2.38-4.47]	4.30[2.36-6.94]	3.69[2.73-4.96]	4.11[2.25-4.94]	3.27[2.60-5.41]	5.08[2.21-6.25]
Coarse	2.84[1.70-4.41]	2.51[2.03-5.47]	3.44[2.05-4.19]	3.88[2.31-6.61]	3.36[2.57-4.44]	3.91[2.14-4.55]	3.22[2.60-5.41]	5.02[2.10-5.92]
Fine	0.26[0.09-0.44]	0.33[0.26-0.66]	0.16[0.03-0.33]	0.33[0.04-0.43]	0.30[0.16-0.50]	0.16[0.11-0.25]	0.12[0.05-0.32]	0.33[0.09-0.42]
Number of Wheezes ‡								
Inspiratory phase								
Total	0.47[0.15-0.57]	0.57[0.31-0.78]	0.76[0.28-0.78]	1.00[0.64-1.33]	0.31[0.19-0.71]	0.62[0.52-0.99]	0.31[0.22-0.38]	0.36[0.23-0.40]
Monophonic	0.32[0.11-0.57]	0.50[0.23-0.61]	0.59[0.24-0.63]	0.71[0.55-0.98]	0.21[0.19-0.64]	0.57[0.32-0.74]	0.23[0.14-0.31]	0.28[0.23-0.33]
Polyphonic	0.04[0.00-0.20]	0.09[0.07-0.16]	0.13[0.04-0.26]	0.14[0.04-0.39]	0.07[0.05-0.24]	0.19[0.02-0.25]	0.07[0.47-0.14]	0.07[0.03-0.07]
Occupation rate (%)	9.3[5.4-13.5]	9.2[7.3-13.3]	16.0[6.1-19.9]	16.8[8.7-32.6]	8.0[3.7-13.1]	12.9[8.0-19.9]	7.2[4.2-8.9]	5.3[3.5-8.2]
Expiratory phase								
Total	0.57[0.43-0.75]	0.83[0.26-1.58]	0.93[0.54-1.48]	1.58[1.02-1.78]	0.64[0.45-0.93]	0.84[0.53-0.91]	0.43[0.28-0.57]	0.57[0.28-0.78]
Monophonic	0.50[0.33-0.57]	0.74[0.23-0.93]	0.59[0.50-1.38]	0.95[0.74-1.27]	0.50[0.40-0.78]	0.75[0.42-0.80]	0.28[0.24-0.50]	0.43[0.24-0.64]
Polyphonic	0.09[0.04-0.24]	0.21[0.06-0.55]	0.12[0.05-0.33]	0.36[0.28-0.52]	0.11-[0.04-0.14]	0.11[0.04-0.16]	0.14[0.03-0.15]	0.14[0.11-0.22]
Occupation rate (%)	6.52[4.43-7.69]	8.30[4.52-11.67	13.1[6.5-24.6]	14.6[9.0-23.7]	6.8[5.1-8.3]	11.1[7.7-11.6]	4.8[3.2-11.0]	5.9[3.5-8.5]

Data are presented as median and [interquartile range] † Analysis without trachea point. ‡ Analysis across all anatomical points.

Table 3. Descriptive characteristics of adventitious respiratory sounds stratified by each one of the chest locations recorded.

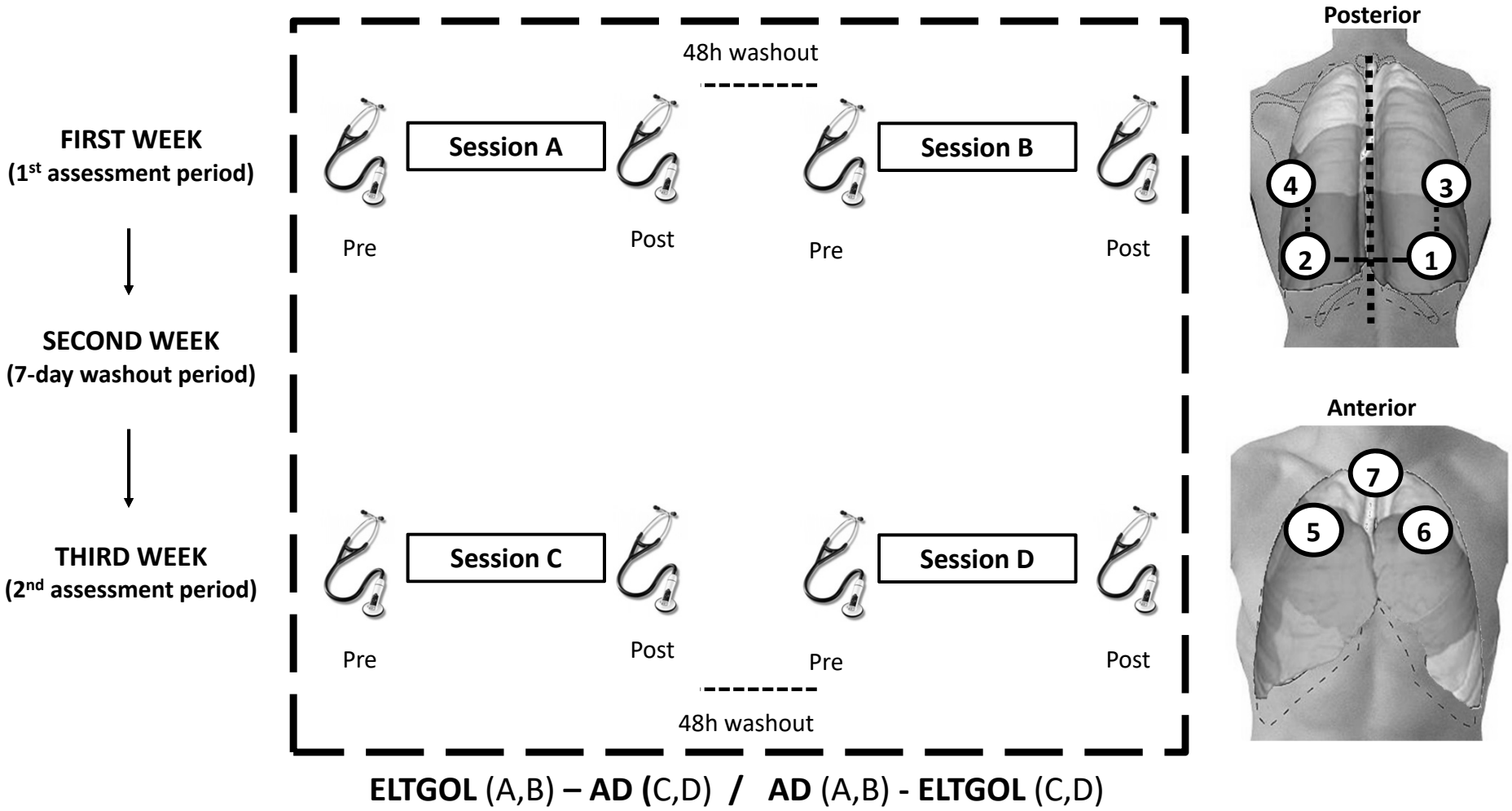
	Anterior regions		**Lateral regions**		**Posterior regions**		**Trachea**	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post
Number of Crackles[†]								
Inspiratory phase								
Total	1.50[1.00-2.66]	2.00[1.06-2.45]	1.73[1.05-2.33]	2.00[1.50-2.66]	1.66[1.05-2.31]	2.00[1.06-2.68]	-	-
Coarse	1.33[1.00-2.00]	1.50[1.00-2.00]	1.50[1.00-2.00]	1.55[1.00-2.00]	1.33[0.75-2.18]	1.55[1.00-2.00]	-	-
Fine	0.25[0.00-0.5]	0.22[0.00-0.50]	0.22[0.00-0.50]	0.25[0.00-2.00]	0.22[0.00-0.50]	0.10[0.00-0.50]	-	-
Expiratory phase								
Total	3.70[2.00-4.66]	3.66[1.76-5.50]	3.00[2.42-5.33]	4.33[2.33-5.91]	3.00[1.80-4.25]	3.83[2.50-5.00]	-	-
Coarse	3.58[1.66-4.50]	3.00[1.66-5.00]	2.87[2.27-4.66]	4.16[2.05-5.92]	2.87[1.60-4.18]	3.29[2.12-4.87]	-	-
Fine	0.25[0.00-0.50]	0.10[0.00-0.50]	0.20[0.00-0.40]	0.00[0.00-0.50]	0.00[0.00-0.25]	0.00[0.00-0.46]	-	-
Number of Wheezes [Ŧ]								
Inspiratory phase								
Total	0.33[0.21-0.80]	0.50[0.17-1.00]	0.25[0.00-0.57]	0.50[0.00-1.00]	0.33[0.00-0.60]	0.50[0.00-1.19]	0.33[0.11-0.50]	0.42[0.15-0.85]
Monophonic	0.33[0.00-0.66]	0.33[0.00-1.00]	0.20[0.00-0.47]	0.33[0.00-1.00]	0.20[0.00-0.40]	0.29[0.00-0.66]	0.25[0.00-0.50]	0.36[0.00-0.54]
Polyphonic	0.00[0.00-0.31]	0.00[0.00-0.33]	0.00[0.00-0.20]	0.00[0.00-0.00]	0.00[0.00-0.24]	0.00[0.00-0.33]	0.00[0.00-0.00]	0.00[0.00-0.54]
Occupation rate (%)	9.7[4.7-17.8]	10.8[3.8-20.6]	5.7[0.0-1.1]	7.4[0.0-16.7]	8.5[0.0-15.2]	7.4[0.0-22.6]	7.0[3.3-10.7]	6.5[3.3-11.7]
Expiratory phase								
Total	0.66[0.00-1.33]	0.67[0.50-1.33]	0.60[0.00-1.15]	0.71[0.05-2.00]	0.40[0.00-0.79]	0.66[0.25-1.33]	0.50[0.31-1.00]	1.00[0.47-1.50]
Monophonic	0.55[0.21-1.00]	0.50[0.27-1.00]	0.50[0.00-1.00]	0.58[0.00-1.62]	0.31[0.00-0.66]	0.50[0.21-1.00]	0.33[0.25-0.64]	0.50[0.20-1.00]
Polyphonic	0.00[0.00-0.33]	0.00[0.00-0.47]	0.00[0.00-0.20]	0.00[0.00-0.31]	0.00[0.00-0.00]	0.00[0.00-0.25]	0.00[0.0-0.25]	0.26[0.00-0.62]
Occupation rate (%)	8.2-[3.9-14.7]	8.3[3.1-16.0]	6.7[0.0-13.1]	6.8[0.6-13.7]	5.2[0.0-9.9]	6.4[2.9-12.4]	7.4[3.4-10.6]	10.6[6.6-13.8]

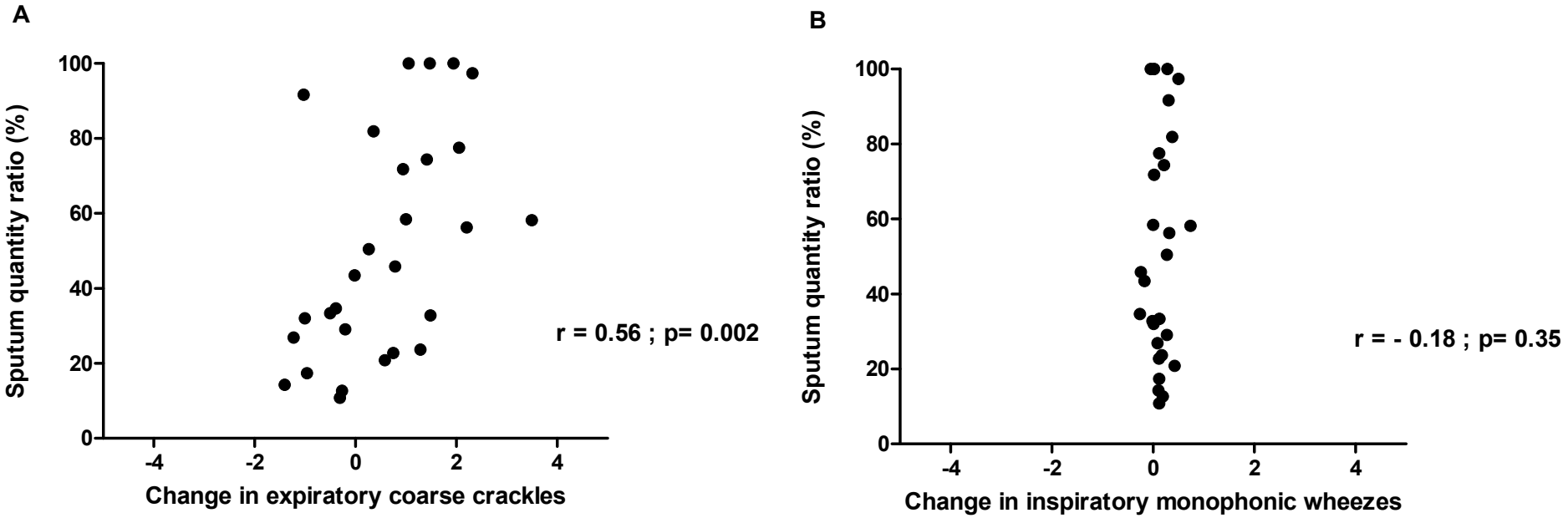
Data are presented as median and [interquartile range]. [†] Analysis without trachea point. [Ŧ] Analysis across all anatomical points.

Table 4. Changes in adventitious respiratory sound after slow-expiratory airway clearance techniques.

Outcome	Pre Mean (SD)	Post Mean (SD)	Mean difference (95%CI)	Pre Median [IQR]	Post Median [IQR]	Median difference (95% CI)	ES (95% CI)
Number of Crackles†							
Inspiratory phase							
Total	1.90 (0.78)	1.99 (0.63)	0.09 [-0.18-0.37]	1.71 [1.29-2.59]	1.96 [1.43-2.30]	0.18 [-0.14-0.36]	0.24 [-0.15-0.62]
Coarse	1.57 (0.68)	1.64 (0.55)	0.07 [-0.17-0.31]	1.49 [1.13-1.87]	1.57 [1.33-1.99]	0.15 [-0.12-0.27]	0.26 [-0.13-0.65]
Fine	0.25 (0.16)	0.33 (0.26)	0.08 [-0.02-0.18]	0.27 [0.08-0.36]	0.33 [0.12-0.42]	0.04 [-0.05-0.14]	0.22 [-0.17-0.61]
Expiratory phase							
Total	3.66 (1.59)	4.31 (2.03)	0.65 [0.13-1.17]	3.38 [2.66-4.56]	4.14 [2.31-5.74]	0.63 [0.10-1.21]	0.40 [0.01-0.79]
Coarse	3.41 (1.52)	3.98 (1.88)	0.58 [0.10-1.05]	3.21 [2.57-4.44]	3.90 [2.27-5.35]	0.55 [0.08-1.05]	0.40 [0.01-0.79]
Fine	0.33 (0.25)	0.35 (0.25)	0.02 [-0.09-0.13]	0.26 [0.15-0.43]	0.33 [0.15-0.49]	0.05 [-0.02-0.16]	0.15 [-0.24-0.54]
Number of Wheezes ₸							
Inspiratory phase							
Total	0.47 (0.31)	0.66 (0.37)	0.19 [0.06-0.31]	0.37 [0.23-0.70]	0.59 [0.32-0.97]	0.17 [0.06-0.31]	0.51 [0.11-0.90]
Monophonic	0.35 (0.24)	0.50 (0.28)	0.15 [0.06-0.23]	0.26 [0.19-0.59]	0.46 [0.27-0.68]	0.14 [0.05-0.22]	0.61 [0.22-1.00]
Polyphonic	0.12 (0.11)	0.15 (0.13)	0.04 [-0.02-0.10]	0.07 [0.05-0.20]	0.10 [0.07-0.24]	0.03 [-0.02-0.09]	0.18 [-0.21-0.57]
Occupation rate (%)	11.2 (8.0)	13.0 (9.3)	1.8 [-1.6-5.2]	8.8 [5.4-15.4]	9.3 [7.4-18.2]	-0.17 [-2.64- 2.13]	0.22 [-0.17-0.61]
Expiratory phase							
Total	0.70 (0.39)	0.96 (0.62)	0.25 [0.08-0.43]	0.57 [0.43-0.93]	0.84 [0.50-1.51]	0.25 [0.04-0.44]	0.45 [0.06-0.84]
Monophonic	0.57 (0.34)	0.72 (0.48)	0.15 [0.02-0.28]	0.50 [0.30-0.74]	0.74 [0.41-0.92]	0.14 [0.02-0.27]	0.37 [-0.02-0.76]
Polyphonic	0.13 (0.10)	0.23 (0.20)	0.10 [0.03-0.17]	0.12 [0.05-0.18]	0.15 [0.07-0.36]	0.08 [0.02-0.16]	0.52 [0.13-0.91]
Occupation rate (%)	9.5 (7.1)	10.6 (8.1)	1.0 [-1.5-3.4]	6.9 [4.8-11.6]	8.8 [6.1-11.7]	0.91 [-0.66-2.96]	0.20 [-0.19-0.59]

† Analysis without trachea point. ₸ Analysis across all anatomical points.


FIRST WEEK
(1st assessment period)
SECOND WEEK
(7-day washout period)
THIRD WEEK
(2nd assessment period)
48h washout
Session A
Session B
Session C
Session D
Pre
Post
Pre
Post
Pre
Post
Pre
Post
48h washout
Posterior
4
3
2
1
Anterior
7
5
6
ELTGOL (A,B) – AD (C,D) / AD (A,B) - ELTGOL (C,D)


A
Sputum quantity ratio (%)
100
80
60
40
20
0
-4
-2
0
2
4
Change in expiratory coarse crackles
r = 0.56 ; p= 0.002
B
Sputum quantity ratio (%)
100
80
60
40
20
0
-4
-2
0
2
4
Change in inspiratory monophonic wheezes
r = - 0.18 ; p= 0.35